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Name of Patentee: Nippon Hoechst Marion Roussel Ltd.
Title: Prolonged Action Preparation of Oxybutynin Hydrochloride

What is Claimed is:

1. A prolonged action preparation of oxybutynin hydrochloride, characterized in that, said preparation contains a sustained release oxybutynin hydrochloride where a pharmaceutical composition containing oxybutynin hydrochloride and an acidic substance is subjected to a sustained release coating.

2. A prolonged action preparation of oxybutynin hydrochloride according to claim 1, characterized in that, said preparation contains 0.1-40 parts by weight of an acidic substance to one part by weight of oxybutynin hydrochloride.

3. A prolonged action preparation of oxybutynin hydrochloride according to claim 1 in which the sustain d

4. A prolonged action preparation of oxybutynin hydrochloride according to claim 1 in which the sustain d release coat is thyl cellulose or a combination of ethyl c llulose with oth r water-insoluble high molecular substance.

5. A prolonged action preparation of oxybutynin hydrochloride according to any of claim 1 to claim 4 in which the amount of the sustained release coat to 100 parts by weight of the pharmaceutical composition containing oxybutynin hydrochloride is 1-100 parts by weight.

6. A prolonged action preparation of oxybutynin hydrochloride, characterized in that, said preparation consists of quick release oxybutynin hydrochloride and the sustained release oxybutynin hydrochloride mentioned in claim 1.

7. A prolonged action preparation of oxybutynin hydrochloride according to claim 6 in which said preparation contains 5-50 parts by weight of quick release oxybutynin hydrochloride to 100 parts by weight of the sustained release oxybutynin hydrochloride mentioned in claim 1.

Detailed Description of the Invention:

[Technical Field of the Invention]

The present invention relates to a prolonged action preparation containing oxybutynin hydrochloride which can be

administered orally.

[Prior Art]

Sustained release preparations are able to reduce the frequency of administration per day and, therefore, they have advantages that patients are liberated from the troublesomeness of taking the drug, that instability of effect of the drug caused by forgetting about taking the drug can be prevented, and that the adverse effect by a quick rise of concentration of the drug in blood can be avoided. They have another advantage that, as a result of keeping the optimum concentration of the drug in blood, the therapy is ensured.

Under the recent circumstance where urinary incontinence of aged people is becoming a social problem, effectiveness of oxybutynin hydrochloride which was developed as a remedy for frequent urination and urinary incontinence has been highly appreciated. Although oxybutynin hydrochloride is quickly absorbed after administration, its half life for disappearance is short and, therefore, said drug must be administered three times a day. In addition, due to a symptom of patients suffering from urinary incontinence, their outing is often difficult which causes inconvenience in their social life.

[Problems to be Solved by the Invention]

In view of the above, there has been a demand for developing a prolonged action preparation where the effect of oxybutynin hydrochloride which is a remedy for frequent urination and

of taking the drug, that instability of effect of the drug caused by forgetting about taking the drug can be prevented, and that the adverse effect by a quick rise of concentration of the drug in blood can be avoided. They have another advantage that, as a result of keeping the optimum concentration of the drug in blood, the therapy is ensured.

Under the recent circumstance where urinary incontinence of aged people is becoming a social problem, effectiveness of oxybutynin hydrochloride which was developed as a remedy for frequent urination and urinary incontinence has been highly appreciated. Although oxybutynin hydrochloride is quickly absorbed after administration, its half life for disappearance is short and, therefore, said drug must be administered three times a day. In addition, due to a symptom of patients suffering from urinary incontinence, their outing is often difficult which causes inconvenience in their social life.

[Problems to be Solved by the Invention]

In view of the above, there has been a demand for developing a prolonged action preparation where the effect of oxybutynin hydrochloride which is a remedy for frequent urination and urinary incontinence is prolonged.

[Means to Solve the Problems]

Under such circumstances, the present inventors have conducted an intensive investigation and have found that, organic acid is added, if necessary, to a pharmaceutical

hydroxypropyl methylc llulos , polyvinyl alcohol or polyvinylpyrrolidone) are added to oxybutynin hydrochloride, the mixture is made into a pharmaceutical preparation such as fine particles, powder, granules, diluted powder, pills or tablets, and the resulting pharmaceutical preparation is subjected to a sustained release coating. Alternatively, oxybutynin hydrochloride powder or oxybutynin hydrochloride dissolved in a solvent such as pure water or in alcohol is homogeneously adhered on the surface of granules by a conventional method using commercially available spherical granules such as Nonparel (registered trade mark; Furointo Sangyo) or Serufia (registered trade mark; Asahi Chemical Industry) and a sustained release coating is applied to the resulting pharmaceutical preparation.

With regard to the coating agent for the sustained release treatment in the present invention, commonly used water-insoluble high molecular substances (such as ethyl cellulose, aminoalkyl methacrylate copolymer, methacrylic acid copolymer S, ethyl acrylate/methyl methacrylate copolymer, polyvinyl chloride and polyethylene), high molecular substances (such as hydroxyethyl cellulose, maleic acid anhydride copolymer and styrene/acryl copolymer), enteric substances (such as cellulose acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, methacrylic acid copolymer, hydroxypropyl methylc llulos phthalat and hydroxypropyl

m thylcellulose acetosuccinate) and fat/ il (such as paraffin, microcrystalline wax, stearyl alcohol, cenol, glycerol fatty acid ester, hydrogenated oil, carnauba wax, bees wax, wood wax, stearic acid, palmitic acid, myristic acid, behenic acid and higher fatty acid) are used. Usually, they are dissolved in an appropriate solvent and the resulting solution is applied to a pharmaceutical preparation by, for example, means of spraying whereupon a coat is formed.

With regard to a sustained release coat, a coat consisting of water-insoluble high molecular substance is particularly preferred and, to be most suitable, ethyl cellulose, a combination of ethyl cellulose with water-insoluble high molecular substance or one or more of the above-mentioned substances may be used as a sustained release coat. When ethyl cellulose is combined with a water-insoluble high molecular substance, 5-100 parts by weight of a water-insoluble high molecular substance may be compounded with 100 parts by weight of ethyl cellulose. Ethyl cellulose having various viscosity is commercially available from Dow or from Hercules. Influence of ethyl cellulose on releasing characteristics of the effective ingredient varies depending upon its viscosity and, preferably, the viscosity of 7-50 cps is appropriate for the sustained release coat of the present invention.

When ethyl cellulose is used as a coating agent, it is dissolved in a solvent usually in a conc ntration of 3-10 parts

or suspended in pure water in a concentration of 5-15 parts by weight and the application of 1-100 parts by weight or, preferably, application of 5-50 parts by weight of the resulting solution or emulsion to 100 parts by weight of a pharmaceutical preparation gives a desired sustained release rate.

With regard to the solvent for coating agent using ethyl cellulose or a combination of it with water-insoluble high molecular substance, one of or a mixture of ethyl alcohol, methanol, isopropyl alcohol, acetone, methyl cellosolve, halogenated hydrocarbon, etc. may be used. Further, when a film coating is applied, various additives may be usually added to a coating solution.

Examples of the additives which may be used in the present invention are surface-active agents such as dioctyl sodium sulfosuccinate, dibutyl sebacate, polysorbate 80, polyoxyethylene hydrogenated castor oil, Tweens, isopropyl myristate, sorbitan monostearate, squalane and polyethylene glycols; plasticizers such as trimethyl citrate, triacetin, propylene glycol, glycerol and medium-chain fatty acid glyceride; and lubricants such as talc, magnesium stearate, calcium stearate, light silicic acid anhydrous, hydrous silicic acid and aluminum hydroxide gel. Examples of the antioxidant which may be used in the present invention are butylhydroxyanisole, dibutylhydroxytoluene, propyl gallate, ascorbic acid palmitate, dl- α -tocopherol, cysteine and

thioglyc rol. Dyes, perfumes, corrigents, etc. may be further added thereto. They are used preferably in an amount of 0.01-50 parts by weight to 100 parts by weight of the sustained release coating agent such as ethyl cellulose.

Incidentally, it has been known that, when thickness of the sustained release coating agent such as a coat formed by a high molecular agent (e.g., ethyl cellulose) is made thick, time lag until initiation of release of the drug is resulted. In order to make the time lag short and, at the same time, to adjust the releasing rate, it is recommended to add a water-soluble substance to the water-insoluble sustained release coating agent such as ethyl cellulose. Examples of the substances which may be used for such a purpose are sucrose, sorbitol, mannitol, sodium and the above-mentioned surface-active agents and polyethylene glycols as well as water-soluble coating agents such as hydroxypropyl cellulose, methylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, aminoalkyl methacrylate copolymer E and polyvinylacetal diethylaminoacetate. The amount of the water-soluble substance used therefor varies depending upon the sustained release coating agent but, usually, 0.1-50 parts by weight is preferably used to 100 parts by weight of ethyl cellulose. Releasing rate can be adjusted by changing the amount and the coat thickness.

When the sustained release preparation is administered to

human being, the preparation gradually moves from stomach to lower areas of intestine. It is said that, at that time, the pH values in stomach, duodenum, jejunum and ileum are 1-3.5, 5-6, 6-7 and 8, respectively and the influence of the pH change on release of the drug is not negligible. In the case of the drug in the preparation of the present invention, its solubility in alkaline region decreases and, therefore, it is predicted to be difficult to ensure the dissolution from the preparation in the lower areas of intestine. In order to solve this problem, the present inventors have conducted an intensive investigation and succeeded in preparing a sustained release preparation of oxybutynin hydrochloride which is not affected by pH.

Examples of the applicable acidic substance are hydrochloric acid, phosphoric acid, acetic acid, lactic acid, adipic acid, ascorbic acid, erythorbic acid, citric acid, gluconic acid, glucono-δ-lactone, aspartic acid, glutamic acid, succinic acid, tartaric acid, fumaric acid and malic acid. Those acidic substances may be used either solely or jointly by combining two or more of them. In addition, phosphoric acid and its salt, ascorbic acid and its salt, citric acid and its salt and tartaric acid and its salt may be used jointly. Further, it is possible to use by combining any of the above-mentioned acids. The amount of such an acidic substance varies depending upon the substances constituting the pharmaceutical composition of oxybutynin hydrochloride but, usually, the

amount may be 0.1-40 parts by weight or, preferably, 1-20 parts by weight to one part by weight of oxybutynin hydrochloride. Such an acidic substance may be used by directly mixing with the pharmaceutical composition of oxybutynin hydrochloride in its powdery state or, after dissolving in a solvent such as pure water or alcohol, the solution is added to the pharmaceutical composition and, after that, said pharmaceutical composition is made into fine particles, powder, granules, diluted powder, pills or tablets by a conventional method. Similarly, the acid either in powder or in liquid may also be adhered to Nonparel or Serufia which is the commercially available spherical granules. The sustained release preparation wherein the solubility is improved as such is evaluated by means of a dissolution test at pH 1.2, 4.0 and 6.8 whereupon it has been found that the resulting one is a preparation which is not affected by pH.

The pharmaceutical preparation according to the present invention in which quick release oxybutynin hydrochloride and sustained release one are combined stands for a preparation where the above-mentioned sustained release oxybutynin hydrochloride is combined with quick release oxybutynin hydrochloride prepared by adding an acidic substance to a pharmaceutical composition in the same manner. A compounding ratio of the quick release material to the sustained release material may be d cid d so as to achieve desired concentration

in blood and duration. In addition, when several kinds of the sustained release oxybutynin hydrochloride substances having different release rate are combined, duration of its concentration in blood can be controlled. In the present invention, the compounding rate of the quick release oxybutynin hydrochloride to 100 parts by weight of total oxybutynin hydrochloride is 5-50 parts by weight or, preferably, 10-40 parts by weight. Shape of the prolonged action preparation of oxybutynin hydrochloride prepared as such is powder, fine particles, granules or pills. It is also possible that pharmaceutical fillers are further added thereto followed by subjecting to a conventional means to give dosage forms such as capsules, separately packed powder, tablets, etc.

[Function and Merit]

The prolonged action preparation of oxybutynin hydrochloride of the present invention obtained as such gives quick rise of oxybutynin hydrochloride concentration in plasma, suppression of maximum concentration in plasma, and duration for long time whereby it is now possible to give a preparation of such a type that may be administered just once or twice daily.

[Examples and Comparative Examples]

The present invention will now be further illustrated by way of the following examples.

Example 1.

(1) Manufacture of Pill A.

Oxybutynin hydrochloride (120 g) and 445 g of lactose were weighed, mixed and sieved through a sieve of 100 mesh. Finely powdered tartaric acid (200 g) and 200 g of powdery sugar were mixed and the mixture was mixed with the powder containing the drug to give powder for spraying. Nonparel 103 (600 g)(Furointo Sangyo) was placed in a CF coater (type CF 360; Furointo Sangyo) and warm air was introduced thereinto together with tumbling. In the meanwhile, 25 g of hydroxypropyl cellulose (HPC-L; Nippon Soda) and 70 g of polyethylene glycol 6000 were dissolved in 500 g of a 2:8 mixture of pure water and ethanol to give a binder solution. The powder containing the main ingredient is sprinkled onto the surface of Nonparel together with spraying of the above solution so that the powder was uniformly adhered thereto whereupon pill A was prepared. This will be called quick release pill A.

(2) Manufacture of Coated Pill A.

Ethyl cellulose (60 g), 12 g of pure shellac and 24 g of hydroxypropyl methylcellulose (TC-5; Shin-Etsu Chemical Industry) were dissolved in 552 g of ethanol and 552 g of methylene chloride to give a coating solution. Pill A (600 g) was placed in a CF coater and the coating solution was sprayed thereon so as to make the amount of ethyl cellulose 10% (w/w) whereupon sustained release coated pill A was prepared.

Example 2.

(1) Manufacture of Pill B.

Nonparel 103 (2,620 g) was placed in a Granulex type GR 5 (Frointo Sangyo) and warm air was introduced thereinto with tumbling and flowing. In the meanwhile, 120 g of oxybutynin hydrochloride, 200 g of citric acid, 20 g of polyethylene glycol 6000 and 40 g of hydroxypropyl cellulose were dissolved in 3,400 g of a 7:3 mixture of ethanol and water with stirring and then 76 g of talc was suspended therein. This solution was sprayed on the surface of Nonparel so that oxybutynin hydrochloride is layered on the surface of Nonparel whereupon pill B was prepared. This will be called quick release pill B.

(2) Manufacture of Coated Pill B.

Ethyl cellulose (Std 10; Dow) (200 g) and 20 g of glycerol fatty acid ester (Myvacet 9-40T; Koyo Mercantile Company Ltd) were dissolved in 1,890 g of ethanol and 1,890 g of methine chloride. The pill B (2,000 g) was placed in a Granulex and a coating was conducted so as to make the amount of ethyl cellulose 10% (w/w) whereupon sustained release coated pill B was manufactured.

Example 3.

(1) Manufacture of Plain Granule C.

Each of 180 g of oxybutynin hydrochloride, 1,010 g of lactose, 700 g of corn starch, 600 g of crystalline cellulose (Avicel PH 101; Asahi Chemical Industry), 300 g of succinic acid and 150 g of carboxymethylcellulose (NS-300; Gotoku Yakuhin Kogyo) was weigh d and they were homogeneously mixed. To the

resulting powder was added a 5% aqu ous solution (1,200 g) of hydroxypropyl cellulose which was separately prepared followed by mixing and the mixture was granulated by a conventional method to give plain granule C. This will be called quick release granule C.

(2) Manufacture of Coated Granule C.

Ethyl cellulose (200 g), 40 g of triethyl citrate and 20 g of polyethylene glycol 6000 were added to 1,850 g of ethanol followed by stirring to dissolve. Talc (40 g) was further added thereto and 1,850 g of methylene chloride were added to the mixture with stirring to give a coating solution. The plain granule C (2,000 g) was placed in a Flow Coater Multi (FML-5; manufactured by Furointo), tumbled and coated to make the amount of ethyl cellulose 10% (w/w) whereupon sustained release coated granule C was obtained.

Example 4.

(1) Manufacture of Plain Granule D.

Oxybutynin hydrochloride (180 g), 729.8 g of lactose, 900 g of crystalline cellulose, 600 g of partially alphatized starch, 300 g of tartaric acid and 230 g of sodium tartrate were homogeneously mixed. A 5% aqueous solution (1,200 g) of HPC which was prepared separately was added thereto followed by subjecting to a conventional treatment whereupon plain granule D was prepared. This will be called quick release granule D.

(2) Manufacture of Coated Granule D.

Ethyl cellulose (210 g), 90 g of aminoalkyl methacrylate copolymer and 3 g of glycerol fatty acid ester were dissolved in 2,849 g of ethyl alcohol and 2,850 g of methylene chloride to prepare a coating solution. Plain granule D (3,000 g) was placed in a Spiral Flow Coater (SFC-5; manufactured by Furointo)and coated so as to make the amount of ethyl cellulose 10% (w/w) whereupon sustained release coated granule D was prepared.

Comparative Example 1. Quick Release Tablets.

Each of 30 g of oxybutynin hydrochloride, 1.572 g of lactose and 180 g of crystalline cellulose was weighed and they were mixed homogeneously. The mixture was then lubricated by adding 18 g of magnesium stearate and compressed to give tablets each weighing 180 mg whereupon quick release tablets were prepared.

Comparative Example 2. Sustained Release Preparation Containing No Acid.

Each of 120 g of oxybutynin hydrochloride, 840 g of lactose, 600 g of crystalline cellulose and 400 g of corn starch was weighed and they are mixed homogeneously. Then separately prepared 5% aqueous solution (800 g) of hydroxypropyl cellulose was added to the above powder and the mixture was kneaded and made into particles by a conventional method. The resulting particles were sieved to remove fine powder and aggregated particles and 500 g of the resulting particles of certain sizes were coated with the following film solution. Formulation of

th film solution was that 50 g of thyl cellulos , 10 g of triethyl citrate and 5 g of polyethylene glycol 6000 were dissolved in 460 g of ethanol. To this solution were added 10 g of talc and 460 g of methylene chloride to give a coating solution. The particles were coated by a conventional method so as to make the amount of ethylene cellulose 10% (w/w) whereupon sustained release coated granules containing no acid were prepared.

[Test Example]

Test Example.

Dissolution test of the prolonged action preparations obtained in the Examples was conducted. In addition, representative preparation formulations were administered to human being and changes in the oxybutynin hydrochloride concentration in blood were measured.

(1) Experimental Methods - Test by a Dissolution Test according to the Japanese Pharmacopoeia, 12th Edition.

A prolonged action preparation was placed in a one-liter flask, then 900 ml of the solution No. 1 (pH 1.2) of the Japanese Pharmacopoeia or a phosphate buffer (pH 6.8) were added thereto and the mixture was warmed at 37℃. The mixture was subjected to a paddle method with 100 revolutions, test solutions were collected after 1, 2, 3, 4, 6, 8, 10 and 12 hours and the amount of oxybutynin hydrochloride was determined by means of a high performance liquid chromatography (HPLC). Then a test in human

being was conducted. Thus, as a comparative example, two quick release tablets (each containing 3 mg of oxybutynin hydrochloride) were administered to volunteers. With regard to a prolonged action preparation, the sustained release preparation (corresponding to 5 mg of oxybutynin hydrochloride) and the quick release preparation (corresponding to 1 mg of oxybutynin hydrochloride) prepared in Example 2 were combined and administered to volunteers whereupon comparison with commercially available preparations was conducted. Blood was collected after 0.5, 1, 2, 3, 4, 6 and 8 hours and centrifuged and the amount of oxybutynin hydrochloride in the plasma was determined by means of an HPLC-ECD method.

(2) Results.

The results are given in Fig. 1 to Fig. 6. Fig. 1 shows dissolution curves of the quick release tablets of Comparative Example 1 at pH 1.2 and 6.8 and dissolution curves of the sustained release preparation containing no organic acid prepared in Comparative Example 2. Thus, although a significant sustained release was noted as compared with the quick release tablets, the dissolution at pH 6.8 was lower than the dissolution at pH 1.2 suggesting that there is a problem. Fig. 2 shows dissolution curves of the preparation obtained in Example 1 at pH 1.2 and 6.8 where it was found that there was no difference between the dissolution data and the preparation showed a sustained release property. Fig. 3 shows dissolution

curves of the pr paration of Example 2 at pH 1.2 and 6.8; Fig. 4 shows dissolution curves of the preparation of Example 3 at pH 1.2 and 6.8; and Fig. 5 shows dissolution curves of the preparation of Example 4 at pH 1.2 and 6.8. In all of those cases, the preparation was hardly affected by pH and showed a sustained release property. In Fig. 6, there is a graph showing the changes in concentration in blood when the quick release oxybutynin hydrochloride (6 mg) prepared in Comparative Example 1 was administered to four volunteers in a hungry state. There is another graph showing the changes in concentration in blood when a capsule (in which a quick release granule C containing 1 mg of oxybutynin hydrochloride and a sustained release coated granule C containing 5 mg of oxybutynin hydrochloride obtained in Example 3 were filled) was administered to hungry volunteers. It is apparent from Fig. 6 that, as compared with quick release tablets, the preparation of the Example gave a prompt rise in its concentration in blood and showed a prolonged action. When biological parameters of the preparation of the Example were compared with those of the quick release tablets, T_{max} was 4-fold, C_{max} was about 1/2 and MRT was 3.6-fold while there was no much difference in terms of AUC whereby a sustained release ability was confirmed even in human being.

Brief Explanation of the Drawings:

Fig. 1 are the graphs showing the dissolution curves of the preparations of Comparative Examples 1 and 2.

Fig. 2 are the graphs showing the dissolution curves of the preparation of Example 1.

Fig. 3 are the graphs showing the dissolution curves of the preparation of Example 2.

Fig. 4 are the graphs showing the dissolution curves of the preparation of Example 3.

Fig. 5 are the graphs showing the dissolution curves of the preparation of Example 4.

Fig. 6 are the graphs showing the concentrations in blood by administration of the preparations manufactured by Comparative Example 1 and Example 3.

In Fig. 1 to Fig. 6

(1) Dissolution Rate

(2) Time

(3) Concentration in Plasma

(4) Quick Release Tablets

(5) Sustained Release Preparation

（塩酸オキシプチニン１ｍｇ相当）を組み合わせてボランティアに投与し、市販製剤と比較した。血液を 0.5、1、2、3、4、6、8時間に採血し、遠心分離後プラズマ中の塩酸オキシプチニンをＨＰＬＣ－ＥＣＤ法にて定量した。

【００２４】②．結果

結果を図１ないし図６に示す。図１に比較例１で示した速溶性の錠剤のｐＨ 1.2とｐＨ 6.8の溶出曲線および比較例２で得られた有機酸を含まない徐放製剤からの溶出曲線を示す。速放錠に比べ若明な徐放性を示すがｐＨ 1.2の溶出に比較し、ｐＨ 6.8では低い値となり問題があることを示唆している。図２は実施例１で得られた製剤のｐＨ 1.2とｐＨ 6.8での溶出曲線で、溶出に差はなく徐放性であることがわかる。図３は実施例２の製剤のｐＨ 1.2とｐＨ 6.8での溶出曲線、図４は実施例３の製剤のｐＨ 1.2とｐＨ 6.8の溶出曲線、図５は実施例４の製剤のｐＨ 1.2とｐＨ6.8の溶出曲線を示す。いずれもｐＨによる影響を受けにくく、徐放性が得られている。図６は比較例１で得られた速放性の塩酸オキシプチニン６ｍｇを空腹時ボランティア４名に投与したときの血中濃度推移を示すグラフである。また、実施例３で得られた塩酸オキシプチニン１ｍｇを含む速放性顆粒Ｃと塩酸オキシプチニン５ｍｇを含む徐放性コーティング顆粒Ｃをカプセルに入れ、空腹時投与したときの血中濃度推移を示す。図から明らかなように、実施例の製剤は速放錠に比較して血中濃度の上昇がすみやかで持効性を示した。実施例の製剤は速放錠と生物学的パラメータを比較すると、Tmaxで４倍、Cmaxは約１／２、ＭＲＴは 3.6倍になり、ＡＵＣはあまり差がなく、ヒトにおいても徐放性が確認された。

【図面の簡単な説明】

【図１】比較例１および２の製剤の溶出曲線を示すグラフ。

【図２】実施例１の製剤の溶出曲線を示すグラフ。

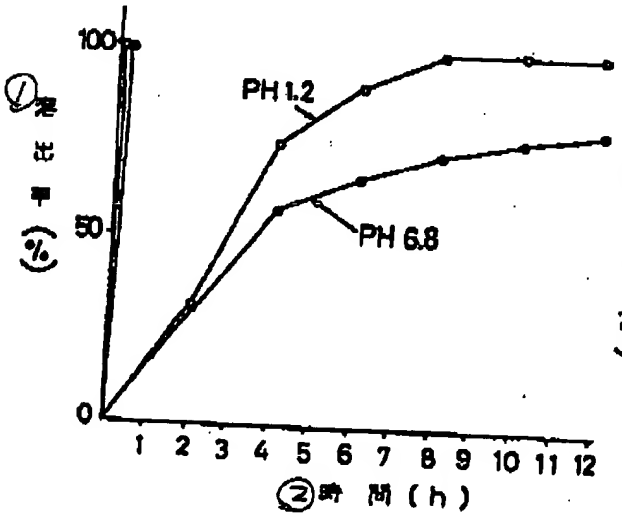
【図３】実施例２の製剤の溶出曲線を示すグラフ。

【図４】実施例３の製剤の溶出曲線を示すグラフ。

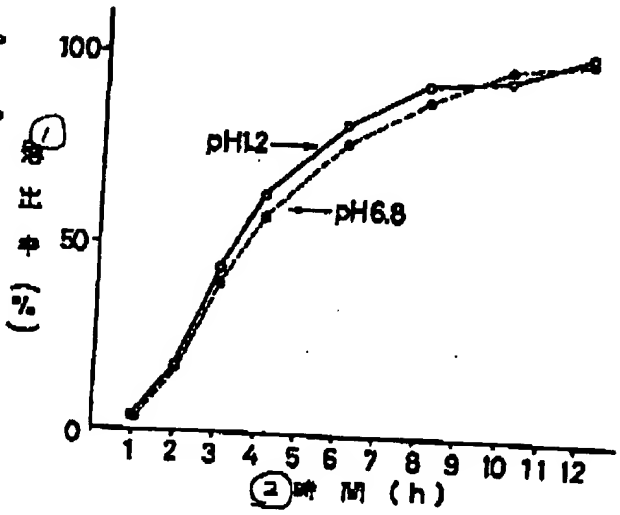
【図５】実施例４の製剤の溶出曲線を示すグラフ。

【図６】比較例と実施例の製剤投与による血中濃度を示すグラフである。

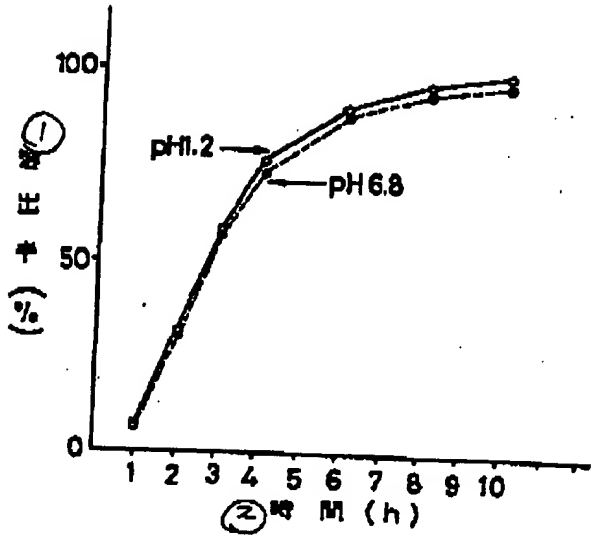
【図１】



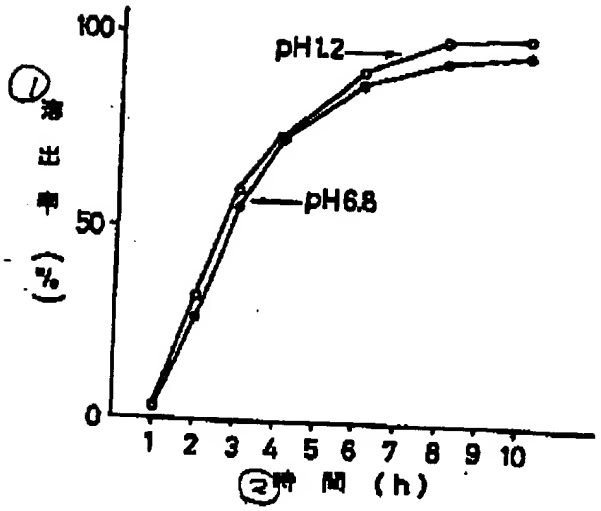
【図２】



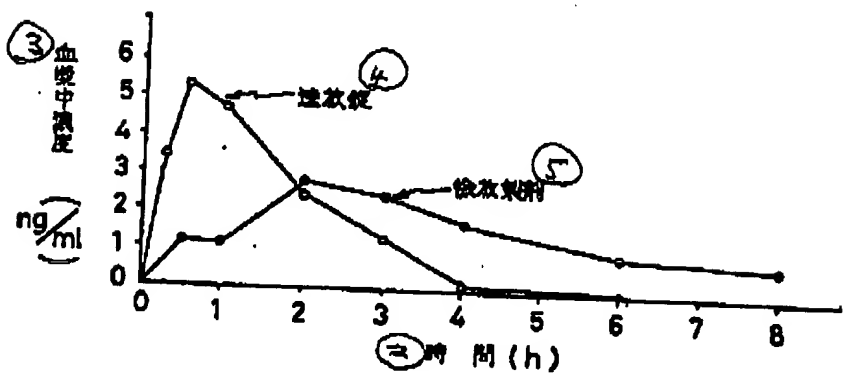
【図3】


100
50
0
① 溶出率 (%)
pH1.2
pH6.8
1 2 3 4 5 6 7 8 9 10
② 時間 (h)

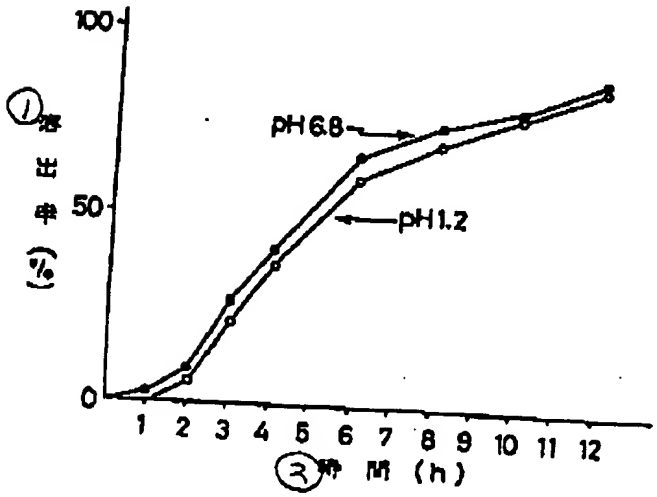
【図4】


100
50
0
① 溶出率 (%)
pH1.2
pH6.8
1 2 3 4 5 6 7 8 9 10
② 時間 (h)

【図6】


③ 血漿中濃度 ng/ml
6
5
4
3
2
1
0
④ 徐放錠
⑤ 徐放製剤
0 1 2 3 4 5 6 7 8
② 時間 (h)

【図5】


100
50
0
① 溶出率 (%)
pH6.8
pH1.2
1 2 3 4 5 6 7 8 9 10 11 12
② 時間 (h)